

Int J Cardiovasc Imaging (2010) 26:173–176
DOI 10.1007/s10554-009-9557-8

EDITORIAL COMMENT

Is size really all that matters? Remarks on size and necrotic core content of atherosclerotic plaques

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Received: 30 November 2009 / Accepted: 4 December 2009 / Published online: 31 December 2009
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Atherosclerotic coronary heart disease remains the leading cause of morbidity and mortality in populations with so-called western lifestyle. During the last two decades intravascular ultrasound (IVUS) allowed us to study the atherosclerotic disease process in the coronary vessel wall in vivo [1–4]. By use of motorized pullback systems, volumetric IVUS data could be obtained that turned out to be ideal for such studies [5–7]. As a result, our insights have been extended from beyond what was known from histopathology and angiographic studies. Serial studies with grey-scale IVUS enriched our understanding of the disease mechanisms involved (e.g., vascular remodelling and progression–regression) and permit an early estimation of the potential effectiveness of new pharmacological anti-atherosclerotic concepts [5, 8, 9].

Intravascular ultrasound assessment of clinically highly successful pharmacological interventions demonstrated some effects on plaque progression–regression and on vascular remodelling; however, these effects on plaque dimensions were relatively small [8]. The discordance between significant clinical benefit and only mild effects on plaque size could be explained by an additional beneficial effect on plaque composition that may lead to stabilisation of the atheroma. Conventional grey-scale IVUS is limited in the assessment of plaque composition [2, 10]. For that reason, a novel approach for radiofrequency (RF)-based analysis of IVUS data was developed which quantifies coronary plaque components and permits the detection of features of plaque vulnerability (e.g., necrotic core and thin-cap fibro-atheroma) [10–13]. As recently demonstrated in mild-to-moderately diseased coronary arterial segments in vivo, volumetric RF-based IVUS analysis shows a relatively high measurement reproducibility for both interobserver and between centre-comparisons [14, 15]. Despite some limitations, studies with RF-based IVUS go beyond the scope of plaque size measurement and may provide additional information on the nature and the “pathology” of coronary atherosclerosis.

Post-mortem studies of coronary arterial specimen previously provided evidence that the necrotic core size and relative necrotic core content of a plaque are features of plaque instability that are related to coronary events [16–18]. Because of the known

Editorial comment on the article of Xu et al.
(doi: [10.1007/s10554-009-9520-8](https://doi.org/10.1007/s10554-009-9520-8)).

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limitations of grey-scale IVUS in the assessment of plaque composition, conventional IVUS could only be used to examine the size of the cavities inside ulcerated ruptured plaques, which were considered to reasonably correspond with the necrotic core volume prior to plaque rupture [1, 3, 6].

In correspondence with grey-scale IVUS data of our own group [1], the volumetric RF-based IVUS data of Xu et al. [19] *published in the present edition of the International Journal of Cardiovascular Imaging*, show that the (absolute) volume of the necrotic core was greater in larger plaques. Kaple et al. [20] recently showed with RF-based IVUS in 90 de-novo coronary lesions that the site of the largest necrotic core was more often proximal to the minimal lumen site where vessel dimensions were larger. They also demonstrated a relation between positive vascular remodelling and greater size of necrotic core [20]. Missel et al. [21] analyzed registry data of 225 patients with non-ST elevation acute coronary syndromes to show that necrotic core volume was significantly larger in patients with elevated cardiac enzymes; they found that the percentage of necrotic core and its ratio to dense calcium were positively associated with increased risk.

In the study by Xu et al. [19] volumetric RF-based (Virtual Histology) IVUS of 224 target lesions showed a significant linear relation between plaque volume and the absolute amount of tissue components. To put it in other words: the greater the plaque, the greater the volume of each plaque component (e.g. necrotic core tissue). However, the authors found no relation between overall plaque volume and the relative content of necrotic core tissue. That is, larger (more advanced) plaques did not show a significantly higher percentage of necrotic core [19], which is consistent with registry data that were recently published by Qian et al. [22].

But is plaque size all that matters for the vulnerability and the necrotic core content of coronary plaques? The data of some other studies actually suggest a somewhat more loose relation between plaque size and the actual amount of necrotic core. The results of the serial multicenter, randomized, placebo-controlled pharmacological intervention trial Integrated Biomarker And Imaging Study-2 (IBIS-2)—for instance—support this idea [23]. The study assessed changes in volumetric

plaque composition as an endpoint to test the effect of the inhibition of the enzyme lipoprotein-associated phospholipase-A2 with darapladib. The placebo group was treated with maximum current therapies (including intense statin therapy) and finally showed non-significant decrease in plaque volume but a significant increase in absolute and relative necrotic core content; darapladib treatment, on the other hand, stopped necrotic core increase [23]. While the design of the IBIS-2 trial is serial, the observational study by Xu et al. has a cross-sectional design (assessment at one time); therefore, these findings may not actually reflect plaque progression, which is a dynamic process over time.

Several factors and mechanisms other than plaque size could co-determine the relative extent of necrotic core tissue; examples may be: acute coronary syndromes; an increased “inflammatory status”; increased major cardiovascular risk factors such as diabetes; and/or genetic factors. Xu et al. [19] performed in their study some subgroup analyses based on such clinical characteristics (patients with and without acute coronary syndrome and diabetes mellitus); but in these (partly rather small) subgroups, findings were essentially similar to the overall population. This is in contrast to the outcomes of several other studies, which suggested a relatively higher necrotic core content in patients with acute coronary syndromes and with diabetes mellitus [24–27].

The analysis of data from large serial IVUS studies with RF-based assessment of plaque composition will be required to obtain further insight into this interesting matter. Optical coherence tomography (OCT), a light-based technique for invasive coronary imaging, permits an even more detailed assessment of coronary plaques at higher resolution [28–30]. As OCT is limited in penetration depth, IVUS and OCT may complement each other [31, 32]. Therefore, the combined use of both techniques in serial trials may significantly advance our knowledge of coronary atherosclerosis and its progression.

There is obviously a strong relation between plaque size and features of plaque vulnerability; however, we would expect that future advanced coronary imaging studies may reveal that the size of the atherosclerotic plaque is not all that matters.

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